The amendments made to replace the wording "vascular damaging agent other than a cytokine releasing anticancer agent" by "tubulin binding agent" are made for reasons of expediency rather than because the applicants agree that the former language was not acceptable. The law on the question of whether an amendment as proposed in the previous response is allowable or not is clearly set forth in the decision in *In re Johnson and Farnham* 194 USPQ 187 which was discussed in the previous response. The Examiner cannot simply state that *Johnson and Farnham* is inapplicable in this case "because the facts are different". The examiner has given no indication as to which facts are different and if any of the facts are different any reason as to why such difference in facts should mandate a different conclusion from that set out in *Johnson and Farnham*. However, in order to avoid the delays in securing the grant of a patent for other subject matter in the application which is clearly patentable, (currently estimated to be in the region of two years) that would be incurred by filing an appeal on this issue, since it seems that this would be needed to have the law applied correctly and without conceding that the subject matter excluded by the amendment made concedes the unpatentability or relinquishment of such intervening subject matter, the applicants have limited their claims for purely pragmatic reasons.

Similarly, although the term is no longer used in the claims, the applicant does not agree that the term "vascular damaging agent" is one that is objectionable under 35 USC 112 second paragraph. These agents are discussed at page 3 lines 25 - 32 of the specification where the meaning of the term is clearly set out as being compounds that induce selective damage to newly formed rather than established vasculature. . One skilled in the art would have no difficulty in determining whether or not a particular material falls within this definition. An applicant is entitled to be his own lexicographer. *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 2003 U.S. App. LEXIS 8651. The Examiner refers to the Blank et al article cited in the Final Rejection. However, this does not seem relevant to the issue. It does not describe vascular damaging agents (particular compounds) but rather a method whereby some vascular damage can be caused by localizing light and a toxin..

For pragmatic reasons similar to those noted above, claim 1 has been limited to exclude inhibitors of nitric oxide action so as to be confined to inhibitors of nitric oxide formation, a term which the examiner accepts as being clear. The amendment to claim 8 is to restore reference to a compound that was inadvertently excluded in response to the previous official action. Claim 25 has been corrected to conform with the description at page 4 lines 30 - 31.

Turning now to the other issues raised under 35 USC 112 second paragraph, the Examiner's objection to the term "amount sufficient to augment the effect of vascular damaging agent (now tubulin binding agent)" in claim 13 is not understood. The word "augment has a clear meaning: "to make (something well or adequately developed) greater, more numerous, larger or more intense" (Webster's New Collegiate Dictionary, 1980 - copy of relevant page enclosed). It therefore encompasses anything that results in an increase irrespective of whether this is additive or synergistic. Whatever the nature of the increase, if there is one the effect has been augmented and the requirement of the claim has been met.

Again, the Applicant believes that the term "substantially simultaneously bet separately" used in claim 14 is clear. The issue here seems to be the use of the word "substantially". However, the courts have recognized that in some cases exact precision is not possible and that the use of words such as "substantially" and "about" is appropriate so as to allow the applicant to secure proper protection for his invention. Thus in *Verve LLC v. Crane Cams Inc.*65 USPQ2d 1051 (Fed. Cir. 2002), the Federal Circuit pointed out that "[i]t is well established that when the term "substantially" serves reasonably to describe the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish the claimed subject matter from the prior art, it is not indefinite." This is the case here. The term "substantially is as precise as the subject matter permits and should be allowed.

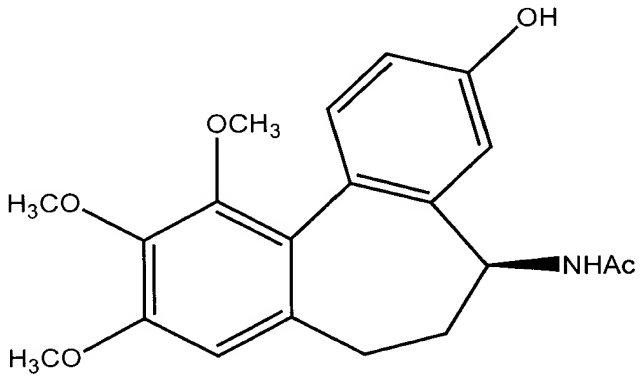
Turning now to the question of priority, the Examiner's reference to two priority applications is not understood. The present application is a national phase entry (371) of a PCT application. That PCT application claimed priority only from British 9903404.3. Since the present application is a371 of the PCT case, it does not claim priority from it because "they" are the same application. The only priority claim is from the British allocation. The only differences between the British application and the PCT application (i.e. the present application), are that the passages at page 6 lines 6 - 18, and pages 7 and 8 and Table 3 on page 9 was not present in the original British application from which priority was claimed. However, the disclosure of these passages is not required to support the composition claims at present on file. The British priority application as filed provides an adequate written description of the invention to meet the written description requirement of 35 USC 112 first paragraph for the subject matter of the present claims. These claims are therefore entitled to a priority date of February 16, 1999. It is noted that the examiner's initial issue on the question of priority was focused on the term "other than cytokine releasing anti-cancer agent" which is no longer present in the claims. It is not clear therefore why the examiner

simply stated that "priority is not granted" in the final rejection when the feature which had provoked the initial raising of this issue was not present in at least newly added claims 22 and 23. In any case, it is submitted that all of the claims presented as a result of the present amendment are fully supported by British application 9903404.3 and entitled to a date of February 16, 1999.

In view of the above submission, it is again submitted that the Tozer reference is not citable under 35 USC 102(b) against the claims of the present application because they are entitled to a date of February 16, 1999 and Tozer was not published until after this date, namely April 1, 1999.

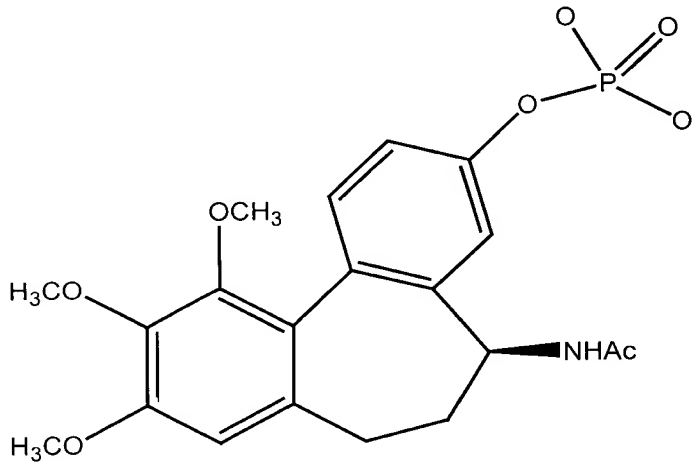
So far as the 35 USC 103(a) rejection is concerned, as noted above, the Tozer reference is irrelevant because it was not published until after the applicable priority date. The Narayanan and Stenger abstracts do describe nitric oxide synthase inhibition by, for example S-alkyl-L-thiocitrullines and certain lysine derivatives respectively. However, neither of these teaches any use that is in any way relevant to the present invention. Narayanan talks of his compounds possibly being of use in the treatment of hypotension. The Stenger abstract gives no particular possible use for its compounds. PCT Publication WO 95/09621 describes the use of a combination of nitric oxide synthase inhibitors and cytokine-releasing anti-cancer agents. However, there is no disclosure of any composition containing a tubulin binding agent, nor is there any reason given as to why one skilled in the art might have thought to replace a cytokine-releasing agent in a composition as described in such PCT publication with any other type of compound, let alone a tubulin-binding agent.

Turning now to the new grounds of rejection, the typographical errors noted by the examiner in claims 8 and 21 have been corrected. So far as claims 24 and 25 are concerned, N-acetylcolchinol has the following structure:.



The compound was known prior to the priority date of the present application and a synthetic method published, for example in R. Brecht, F. Haenel und G. Seitz "Dihydrocolchicine 8,12-Endoperoxide: A Novel Starting Material for Convenient Syntheses of the Allocolchicinoids N-Acetylcolchinol O-Methyl Ether and Androbiphenyline" Liebigs Ann./Recueil 1997, 2275-2279 and Shi, Q.; Chen, K.; Morris-Natschke, S. L.; Lee, K.-H. (1998). "Recent Progress in the Development of Tubulin Inhibitors as Antimitotic Antitumor Agents." *CURR. PHARM. DES.* **4**, 219-248.

However, as noted in the amendment set out above, it was in fact intended to refer to N-acetylcolchinol-O-phosphate in claim 25. As noted page 4 line 30, this is a pro-drug of N-acetylcolchinol. This phosphate has the structure:



A description and synthesis of the phosphate was published in PCT Publication WO 99/02166 which was published on January 21, 1999. (See Example 1)

Claim 22 has been cancelled in this amendment. However, it is submitted that the application as filed clearly supported this claim. The opening paragraph of the application states that the invention is a combination of a nitric oxide inhibitor and a compound causing vascular damage. Page 3 line 32 clearly states that antibodies targeted to vasculature fall within this definition.

The examiner's comments in the first complete paragraph on page 6 of the final rejection are not understood. The second sentence correctly notes that claim 23 - 25 relate, as does revised claim 1, to a combination of tubulin-binding agents and an inhibitor of nitric oxide formation. However, the third sentence refers to anti-vascular antibodies, which are

not relevant to these claims. The invention as now claimed is a combination of an inhibitor of nitric oxide formation and a tubulin binding agent. This combination is clearly described in the application as filed and shows that the applicant had possession of the invention at the time the application was filed, and indeed at the time the British application from which priority is claimed was filed. Both the British application and the PCT application describe the invention as being a composition combining two essential components. The opening paragraph of both states:

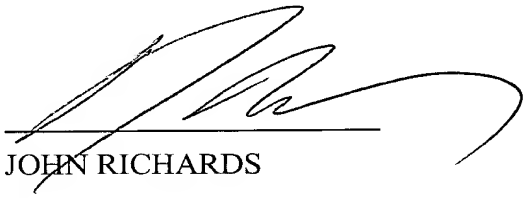
> This invention relates to a method for treating diseases involving active angiogenesis, to compositions useful for the treatment of diseases involving angiogenesis ... In one aspect of the invention the method involves the administration to a mammal of an inhibitor of nitric oxide in combination with a compound inducing vascular damage.

This clearly shows that the applicant had possession of the idea of using generic classes of materials at the time of filing the applications. That he had in mind the use of a subgeneric group of vascular damaging agents, namely tubulin binding agents is shown by his statement at page 3 lines 27 -30 discussing vascular damaging agents stating "Such agents include tubulin-binding agents, for example the combretastasins ...". Further confirmation of this is shown by original claim 3 which referred to the vascular damaging agent being "a" tubulin-binding agent, clearly showing that the inventor had possession of the concept of the use of materials falling within the genus of tubulin-binding agents.

So far as the final paragraph of the final rejection is concerned, the examiner seems to have misunderstood the role of the N-acetylcolchinol and its pro-drug. These are tubulin-binding agents not nitric oxide inhibitors. They are therefore used in combination with nitric oxide inhibitors not with tubulin-binding agents as suggested by the examiner. Irrespective of their precise role, however, it appears that the Examiner questions their availability at the filing date of the present application. As noted above, N-acetylcolchinol and its prodrugs were known prior to the priority date of the present application, at least from the publication of PCT Publication WO 99/02166. It is therefore submitted that the enablement requirement of 35 USC 112 first paragraph has been met.

In view of the foregoing it is believed that this application is now in order for allowance and reconsideration of the final rejection with a view to the issue of a early action to this end is respectfully solicited. If the Examiner believes it would be useful to discuss this matter either personally or in a telephone interview, he is requested to let us know so that this can be arranged.

Respectfully submitted,



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Appendix

1. (Amended) A composition for the treatment of a disease involving active angiogenesis which comprises a **tubulin binding** [~~vascular damaging~~] agent [~~other than a cytokine releasing anticancer agent~~] together with an inhibitor of the formation [~~or action~~] of nitric oxide in a mammalian system.

2. (Amended) A composition for the damage of the formation of new vasculature by angiogenesis comprising a combination of a **tubulin binding** [~~vascular damaging~~] agent [~~other than a cytokine releasing anticancer agent~~] and an inhibitor of nitric oxide synthase in an amount sufficient to augment the effect of the **tubulin binding** [~~vascular damaging~~] agent.

8. (Amended) A composition according to claim 4 wherein the derivative of cutrulline is selected from L-thiocitrulline, **L-homothiocitrulline** or an S-alkylthiocitrulline.

10.(Amended) A composition according to claim 1 wherein the composition is in the form of a kit, one part of the kit comprising the **tubulin binding** [~~vascular damaging~~] agent and the second part of the kit the nitric oxide inhibitor.

13 (Amended) A method of treatment for a mammal having a disease involving active angiogenesis, said method comprising administration of a **tubulin binding** [~~vascular damaging~~] agent [~~other than a cytokine releasing anticancer agent~~] and an inhibitor of formation of nitric oxide in an amount sufficient to augment the effect of the **tubulin binding** agent [~~vascular damaging~~].

14.(Amended) A method according to claim 13 wherein the **tubulin binding** [~~vascular damaging~~] agent and nitric oxide inhibitor are administered substantially simultaneously but separately to the mammal under treatment.

21.(Amended) A composition according to claim 4 wherein the derivative of citrulline is S-methyl-L-**thiocitrulline** [~~thiocityrulline~~].

24.(Amended) A composition according to claim [~~23~~] **1or2** wherein the tubulin binding

agent is selected from N-acetylcolchinol and its prodrugs.

25.(Amended) A composition according to claim [~~23~~] **1 or 2** wherein the tubulin binding agent is N-acetylcolchinol-O-phosphate..